Effects of Duloxetine in Treatment-Refractory Men with Posttraumatic Stress Disorder

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Abstract

Introduction: Although there is evidence that selective serotonin reuptake inhibitors provide some benefit in the treatment of post-traumatic stress disorder (PTSD), most meta-analytical reviews have concluded that effect sizes are small and, moreover, that there may be relatively little benefit for some populations (e.g., combat veterans with co-morbid major depression, MDD). This study aimed to evaluate the effectiveness and tolerability of the dual reuptake inhibitor duloxetine in the treatment of PTSD and co-morbid MDD.

Methods: Twenty-one treatment refractory, male, combat-related patients with PTSD and co-morbid MDD were enrolled in a naturalistic study and twenty completed the trial. Duloxetine was given between 60 and 120 mg daily over 8 weeks.

Results: Duloxetine led to a significant improvement of PTSD-characteristic symptoms as well as co-morbid MDD. Duloxetine effectively reduced nightmares, which is important because decreasing nightmares has been associated with improved sleep in PTSD.

Discussion: The results of this naturalistic study suggest that duloxetine is an effective and well-tolerated treatment for patients with PTSD and co-morbid MDD. These initial results need to be extended to the study of women with PTSD.

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Introduction

The definition of post-traumatic stress disorder (PTSD) in DSM-IV [1] links a specific syndrome, which is characterized mainly by symptoms of re-experiencing, avoidance and hyperarousal with traumatic events that are distinguished from ordinary stressful life events. Epidemiological surveys in the United States from the National Vietnam Veterans Readjustment Study of a representative sample of 1200 veterans showed that 18.7% of the veterans had developed combat-related PTSD during their life times [18]. Similar rates of PTSD have been documented in Veterans of Operations Enduring Freedom and Iraqi Freedom (OEF/OIF) [30,53] with high rates of self-perceived need for treatment [51]. Similar rates of PTSD with a life-time prevalence of approximately 8% are found in people with civilian trauma [29]. The increased morbidity [25,33], disability [52,60] and mortality [8] associated with PTSD call for increased efforts to develop more informative models for testing pathophysiological and treatment hypotheses. Studies report that approximately 33% of individuals exhibit a co-morbidity of PTSD and major depressive disorder (MDD) [21]. This co-morbidity enhances the risk for suicidal behavior [43] and has a negative impact on treatment outcome with increased illness burden, poorer prognosis and delayed response to treatment [9,19–21,27, 34,41,45,46,54,57,59]. This highlights the need to investigate the relevance of novel medications in order to decrease the devastating impact of these disorders on public health.

There have been significant advances in the pharmacotherapy of patients with PTSD, and certain medications, e.g., selective serotonin reuptake inhibitors are considered first-line treatment for adult PTSD [54] and are FDA approved antidepressants to treat PTSD. A substantial number of patients, however, does not show a satisfactory treatment response [48], in fact, remission rates for sertraline, the only FDA approved antidepressant to treat PTSD are only about 25% [10] and therefore there is a need for additional research about how to enhance effectiveness of the existing treatment strategies for PTSD [16]. It was

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shown that pharmacotherapy improves quality of life measures but is only somewhat effective in reducing symptoms of depression and anxiety, which are frequently found in patients with PTSD. In the absence of knowledge about the regulation of neurobiological systems in PTSD, it is difficult to directly link the efficacy of these medications to the neurobiology of the disorder, which may have prevented the development of more efficacious medications for this disorder.

Thus far, treatment development for PTSD has been opportunistic and has not been based on the increasing knowledge of the neurobiology of PTSD. To date only serotonergic agents are approved for the treatment of PTSD. Several lines of evidence, however, have also linked norepinephrine to the neurobiology and the phenotype of PTSD [32], and noradrenergic compounds have shown efficacy in reducing symptoms of PTSD such as anger and irritability [49,55], hyperarousal [61] or nightmares [39], even though not unequivocally [11,38,42,56]. Taken together, this preliminary evidence suggests that agents with a broader mechanism of action may be superior compared to single monoamine reuptake inhibitors. Duloxetine [LY248686, (+)-(*S*)-*N*-methyl-3-(1-naphthyloxy)-3-(thiophen-2-yl)-propan-1-amine] is a potent dual reuptake inhibitor of serotonin and norepinephrine (SNRI) with comparable affinities to both transporter sites [28]. Duloxetine is currently approved for the treatment of major depressive disorder (MDD) [3,26], with a daily dose between 40–60 mg [36].

To date, there are only two case reports with inconclusive results about the use of duloxetine in the treatment of PTSD [14,24]. These initial reports call for additional studies to evaluate the role of duloxetine in the treatment of PTSD. Therefore, we decided to use an observational study design as the logical next step to evaluate the potential role of duloxetine in PTSD. Considering the neurobiology of PTSD with an important role for both serotonin and norepinephrine [32], we predicted that a compound that affects both serotonin and norepinephrine, will be effective in the treatment of PTSD.

Patients and Methods

Patients

Twenty-one men with chronic, treatment-refractory, combat-related PTSD were recruited from the PTSD clinic at the Veterans Affairs Connecticut Healthcare System (VACHS) between February 2007 and January 2008. The VA Human Subject Subcommittee (HSS) and the Yale Human Investigation Committee (HIC) approved the study protocol, and written informed consent was obtained from all participants after the purpose of the study and the study design, as well as risks and benefits had been explained. Patients met the criteria for PTSD as determined by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [44], and had a minimum score of 50 on the Clinician-Administered PTSD Scale (CAPS) [4]. All patients met diagnostic criteria for a current MDD and most of them also had a history of MDD. All patients were considered treatment refractory and had at least two failed adequate antidepressant trials before entering this study. Previous antidepressant medication was discontinued and switched to duloxetine after a washout period of up to 6 days between treatments. Duloxetine was given as monotherapy. No concomitant medications or standardized psychotherapy were allowed during the trial.

Study design

Participants received oral duloxetine as monotherapy for 8 weeks in an open-label study design in a daily dose between 30–120 mg. All patients started treatment with 30 mg for the first week, followed by 60 mg for two weeks, and thereafter the dose was gradually increased up to 120 mg daily in a flexible dosing regime, which was adjusted according to the clinical response. Those patients who showed a positive treatment response to duloxetine continued treatment after the trial.

Behavioral assessments

The primary outcome measure was the PTSD Checklist (PCL-C) [5], a 17-item assessment tool based on DSM-IV criteria for PTSD, administered at baseline and at the end of the 8 weeks trial. Secondary outcome measures included the Hamilton Anxiety Scale (HAM-A) [23], the Montgomery Asberg Depression Rating Scale (MADRS) [40], and the Clinical Global Impression of Severity Scale (CGI-S) [22], and were administered weekly. Adverse events were monitored weekly using the UKU Side Effect Rating Scale [35]. Patient responder status at endpoint was defined as a decrease of 30% or more from baseline to week 8 on the PCL-C score. Patient remission status was defined as decrease of 30% or more on the PCL-C, in addition to a total score of 10 or less on the HAM-A at endpoint [2].

Statistical analysis

A repeated measures analysis of variance (ANOVA) across the nine time-measures was used to examine effects of the intervention. The reported significance levels reflect the Greenhouse-Geisser correction for sphericity and Bonferroni corrected paired t-tests was used to determine the time course of change. Results were considered statistically significant at $p < 0.05$, and corrected p values are reported.

Results

We recruited 21 male veterans with combat-related PTSD into the study. One patient withdrew his consent after the initial dose of the study medication, and his data were not included in the analysis. Therefore, data of 20 patients were available for the analysis (**Table 1**). At the last visit, one patient was taking 60 mg, five patients 90 mg, and fourteen patients were taking 120 mg duloxetine daily.

Table 1 Demographic characteristics (n = 20).

age (years), mean ± SD		52.6 ± 6.8
ethnicity (n)	caucasian	19
	African American	1
co-morbidity (n)	major depressive episode	20
	past depressive episode	14
	history of alcohol abuse	10
	other substance use disorder	8
	panic disorder	10
	specific phobia	6
combat experience (n)	Vietnam	16
	Gulf war	2
	OIF/OEF (Iraq/Afghanistan)	2
combat exposure scale*, mean ± SD		27.9 ± 5.0

*3 missing

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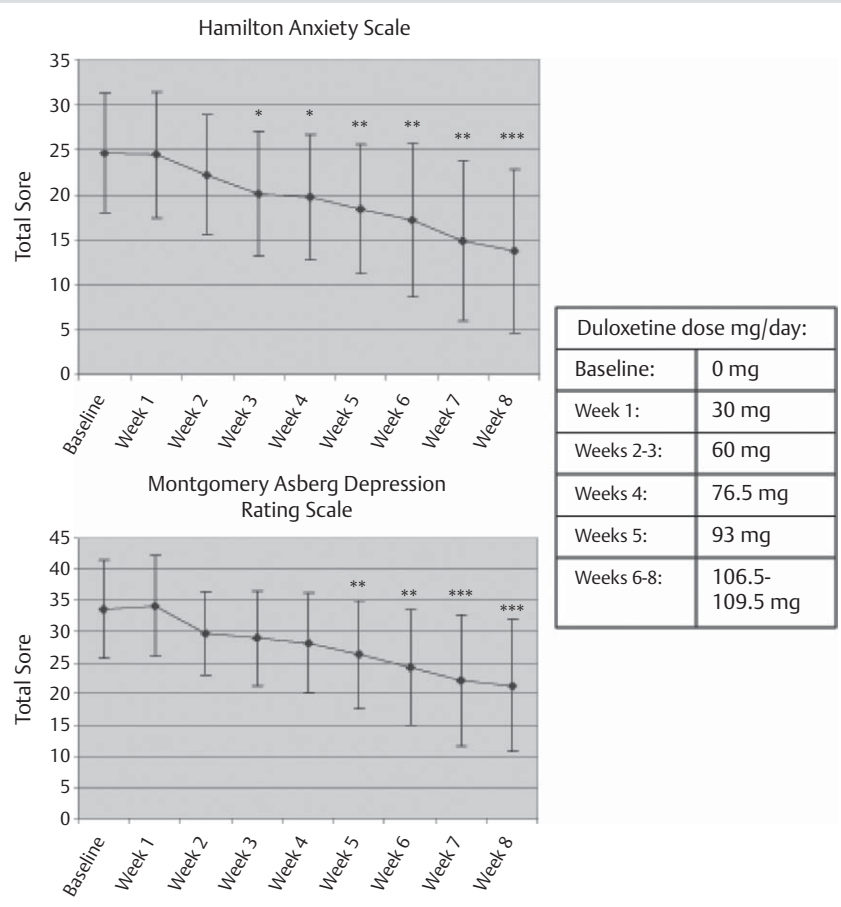

Duloxetine dose mg/day:	
Baseline:	0 mg
Week 1:	30 mg
Weeks 2-3:	60 mg
Weeks 4:	76.5 mg
Weeks 5:	93 mg
Weeks 6-8:	106.5-109.5 mg

Fig. 1 The effect of duloxetine on Hamilton anxiety scale (HAM-A) and Montgomery Asberg depression rating scale (MADRS) by week of treatment, and the average duloxetine dosage. Duloxetine had a statistically significant positive effect on HAM-A and MADRS scores over time. Values are given as mean ± standard deviation. Post-hoc paired sample t-tests with Bonferroni correction for multiple comparisons compared baseline with each of the follow-up weeks, demonstrating improvement with time on all the behavioral scales. The statistical significance was divided into three levels: $^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$.

Table 2 Adverse effects of duloxetine documented with the UKU adverse events scale. UKU grading of severity: 1 = mild, 2 = moderate, 3 = markedly. The highest UKU severity grade across time points was used to calculating the mean. The table includes all adverse events reported by more than one participant.

Adverse events	n	%	UKU grading (Mean ± SD)
increased dream activity	13	65	1.9 ± 0.6
sleep disturbance	11	55	1.7 ± 0.6
increased fatigability	11	55	2.1 ± 0.8
sleepiness/sedation	10	50	2.2 ± 0.8
diminished sexual desire	9	45	2.1 ± 0.9
sweating	9	45	2.0 ± 0.7
reduced salivation	8	40	1.6 ± 0.7
erectile dysfunction	7	35	2.1 ± 0.9
ejaculatory and orgastic dysfunction	7	35	2.0 ± 0.8
photosensitivity	5	25	1.4 ± 0.6
tension/inner unrest	5	25	1.2 ± 0.5
dizziness	5	25	1.2 ± 0.5
concentration difficulties	4	20	1.8 ± 0.5
depression	4	20	1.8 ± 0.5
diarrhea or micturition disturb.	4	20	1.5 ± 0.6
emotional indifference	3	15	2.3 ± 0.6
nausea	3	15	1.0 ± 0.0
weight loss	2	10	1.5 ± 0.7

Treatment with duloxetine had significant behavioral effects as documented in changes on all the behavioral rating scores. The primary outcome measure PCL-C dropped significantly from baseline to follow up at week 8 (64.1 ± 10.2 versus 48.1 ± 11.9, $t(18) = 7.0$, $p < 0.001$). Evaluation of the effects of duloxetine on secondary outcome measures (**Fig. 1**) using a repeated measures ANOVA showed statistically significant decreases in the total scores on the HAM-A ($F_{0,8} = 16.3$, $p < 0.001$), MADRS ($F_{0,8} = 15.2$, $p < 0.001$), and CGI-S ($F_{0,8} = 9.0$, $p < 0.001$). These results indicate a positive effect of duloxetine on symptoms of PTSD, anxiety and depression. At the end of the eight-week trial, eight patients (42%) were considered responders, and four patients (21%) met remission criteria.

Adverse events

Adverse events (**Table 2**) were generally mild and transient, and none of the patients discontinued the treatment study prematurely because of adverse events. The most prevalent event was increased dream activity without nightmares. The dreams were described as pleasant and sometimes puzzling, with enhanced visual clarity, vividness and color.

Discussion

To the best of our knowledge, this is the first report on the effects of duloxetine in a group of chronic, treatment refractory patients with combat-related PTSD and co-morbid depression. Duloxetine displayed beneficial effects on the PTSD-characteristic symptoms, as well as on anxiety and depression symptoms. Duloxetine showed a rapid onset of action, and improvement was progressive and sustained on all outcome measures during the entire eight-week trial. No long-term data on the effects of duloxetine as a maintenance treatment for PTSD are currently available.

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The criteria for treatment response on PTSD symptoms were met by 42% of the patient sample, and the criteria for remission were met by 21% at the last study visit. Previous acute treatment trials using other antidepressants than duloxetine showed that patients with combat related PTSD are more difficult to treat with pharmacotherapy than patients with a history of civilian trauma [15]. Therefore, the data presented herein are encouraging and call for further evaluation of duloxetine in this patient population.

The underlying mechanisms that contributed to the beneficial effects of the dual reuptake inhibitor duloxetine need some discussion. It appears likely that antidepressants ultimately alter homeostasis or allostasis through complex signaling pathways that affect transcriptional events, the activity of enzymes at the cellular membrane, and patterns of neuronal systems activation and connectivity [37]. It appears that the behavioral effects of norepinephrine and serotonin have considerable overlap such that augmenting levels of any one may have antidepressant and anxiolytic effects, and increasing synaptic levels of more than a single neurotransmitter may be synergistic [58]. Cross-talk between norepinephrine neurons and serotonin neurons has been documented such that increased norepinephrine stimulates serotonin release, and serotonin release at norepinephrine neurons reduces norepinephrine release. Further study of patterns of reciprocal interaction and cross-talk between these systems may allow us in the future to understand the balance of activity of monoamine systems and tailoring therapy [6,7]. Duloxetine not only demonstrated its efficacy on depression and anxiety symptoms, which are frequently found in patients with PTSD but was also effective in the treatment of symptoms including re-experiencing, avoidance and hyperarousal which define PTSD and have been linked to norpepinephrine dysfunctions [32].

Regarding the tolerability of duloxetine, the majority of patients reported increased dream activity but a rapid and sustained improvement of their nightmares. This could bear out to be an important improvement for the treatment of PTSD, since sleep disturbances and nightmares occur in up to 70% of patients with PTSD [17], and decreasing nightmares has been found to improve sleep [31]. We found a lower rate of nausea, but a higher rate of sexual dysfunctions compared to other studies of duloxetine [12,47,50]. The higher rate of sexual dysfunctions could be explained in that we studied an all-male, sexually active subject population, and previous studies have found significantly greater impairment of SSRIs and SNRIs on sexual functions in men relative to women [13]. Notably, the occurrence of unwanted duloxetine-associated side effects was reported predominantly during the early phase of the treatment, side effects were generally short-lived and did not lead to premature termination of the treatment.

There are several strengths but also limitations in this observational study that need to be considered in the interpretation of the results. We studied a relatively small group of men with chronic PTSD who were homogeneous regarding their trauma histories. All patients were highly symptomatic and had co-morbid major depression. All of them were treatment-refractory and had at least two failed antidepressant trials before entering this study. The study design, however, is limited by the lack of a control condition and the fact that we studied only men. Therefore results cannot be generalized and need replication in larger scale trials with appropriate control conditions, i.e., placebo or an active comparator, as well as a call for replication in female PTSD patients. Moreover, we studied a group of chronic, treatment-refractory patients with combat-related PTSD and therefore it is of interest to extend these results to patient populations with other trauma histories and shorter duration of the illness. Furthermore, like in many other treatment trials in PTSD, we evaluated the effects of duloxetine during only a relatively short period of eight weeks and therefore additional data about duloxetine's role in the long-term treatment are needed. Also, it would be of interest to know whether administration of duloxetine in the immediate phase after trauma exposure could prevent the development of the full clinical syndrome of PTSD. To date, the presented data, although preliminary, suggest that duloxetine might be a useful treatment option for PTSD.

Altogether, duloxetine appears to be an effective and well-tolerated treatment for PTSD. Moreover, whereas the effects of duloxetine were similar to those of other currently available antidepressants, our data suggest its superiority in controlling high levels of anxiety and depression, which characterize many patients with PTSD. Next steps in the evaluation of duloxetine in PTSD should include larger trials comparing its effects to placebo and active comparators, as well as proof of concept studies linking together the neurobiology of PTSD with the mechanism of action of this novel antidepressant.

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